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(54) **Production of sterile solutions**

(57) Apparatus for producing sterile pyrogen-free aqueous solutions for medical use comprises a reverse osmosis unit for producing pyrogen-free water, means for mixing the pyrogen-free water with a fluid concentrate, deaeration means for removing air from the mixture and sterilisation means for sterilising the mixture.

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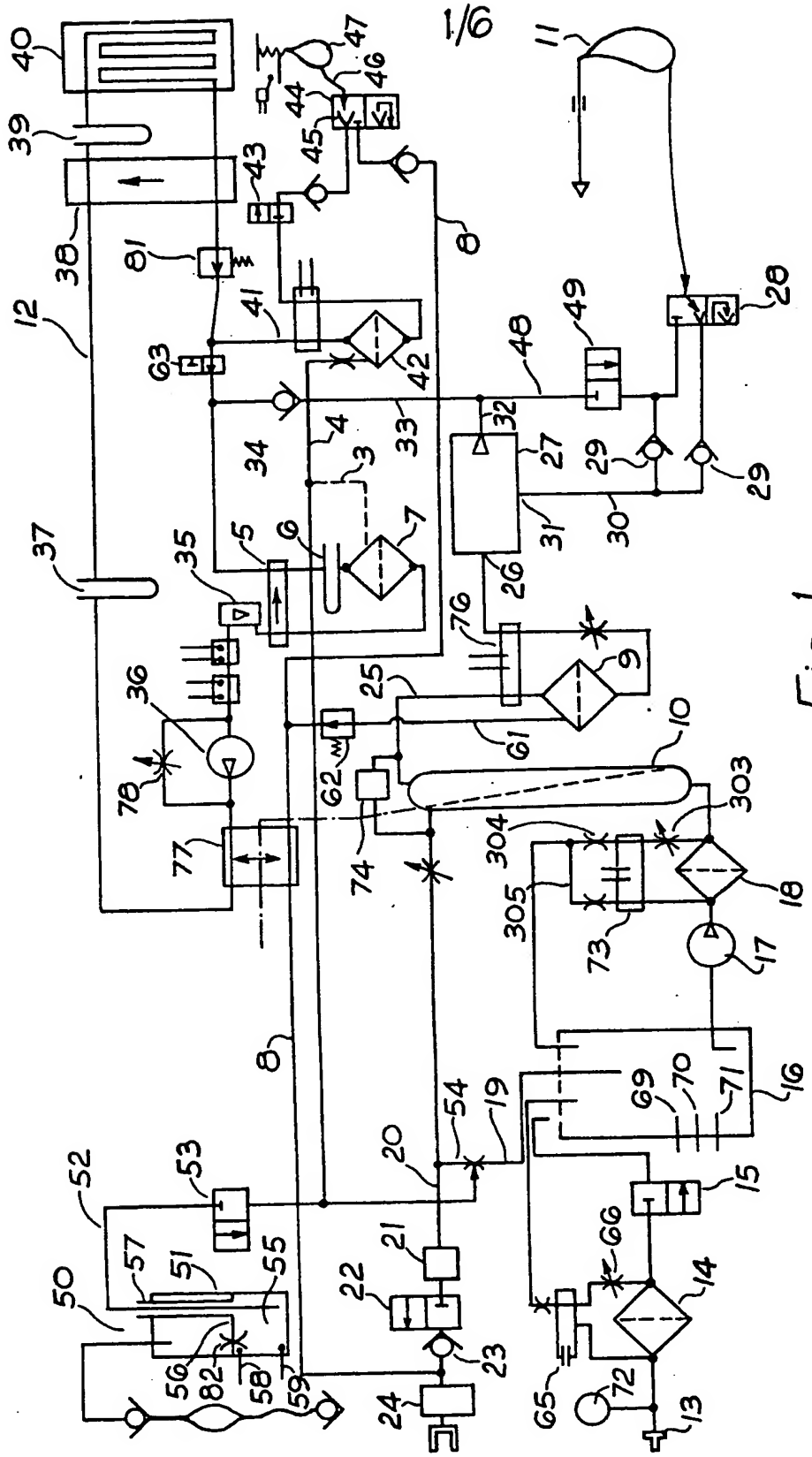

Fig. 1.

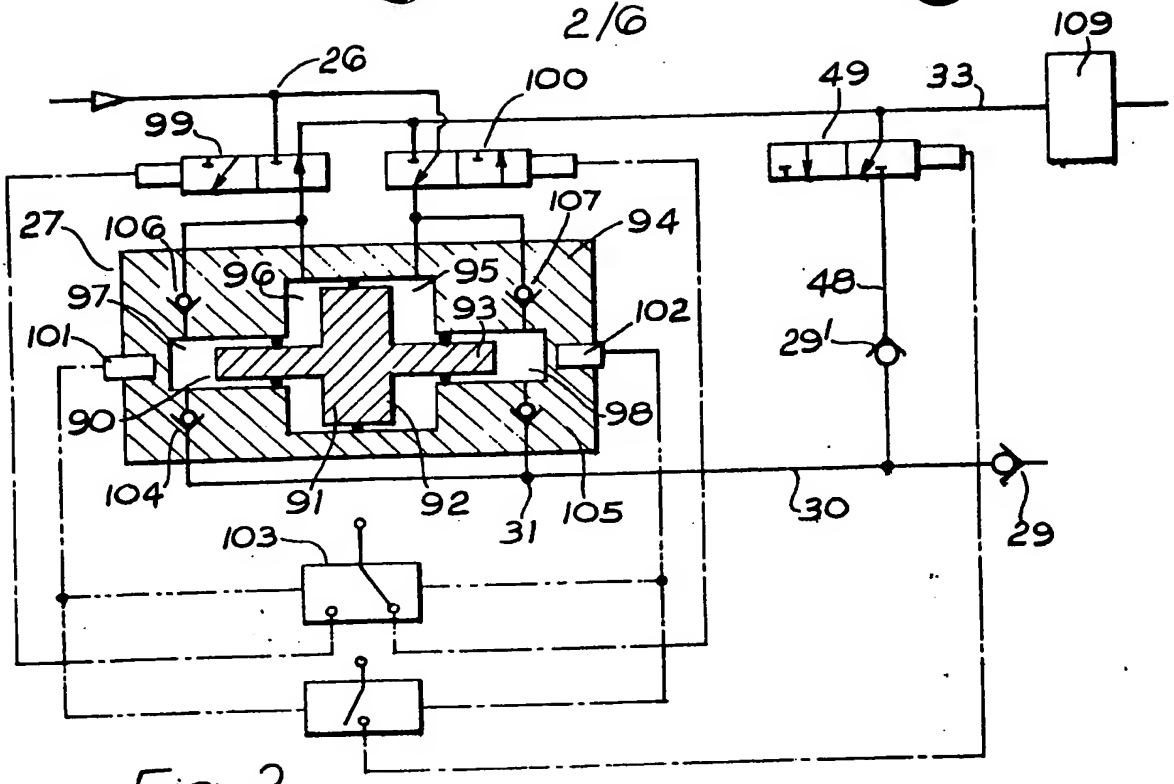

Fig. 2.

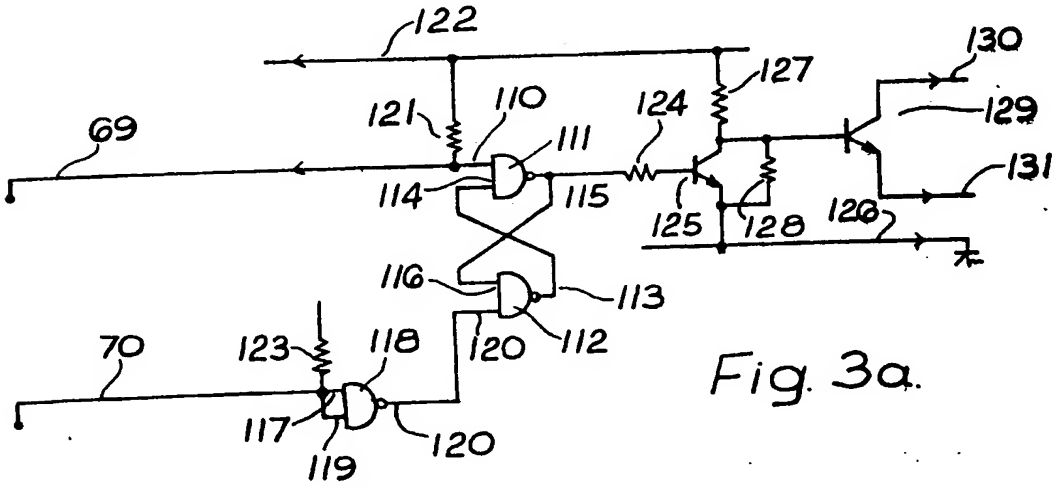

Fig. 3a.

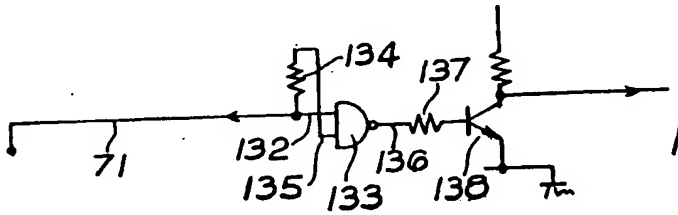

Fig. 3b.

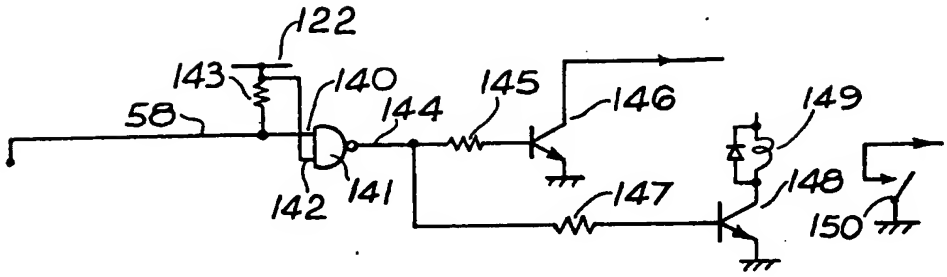

Fig. 4a.

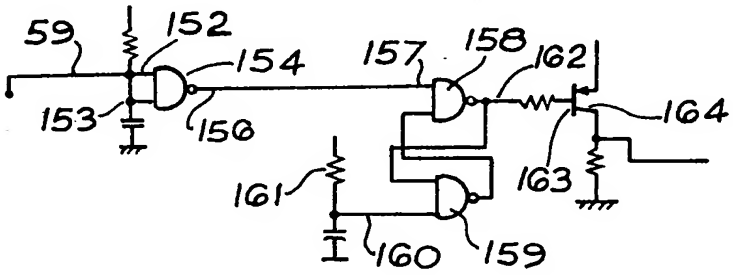

Fig. 4b.

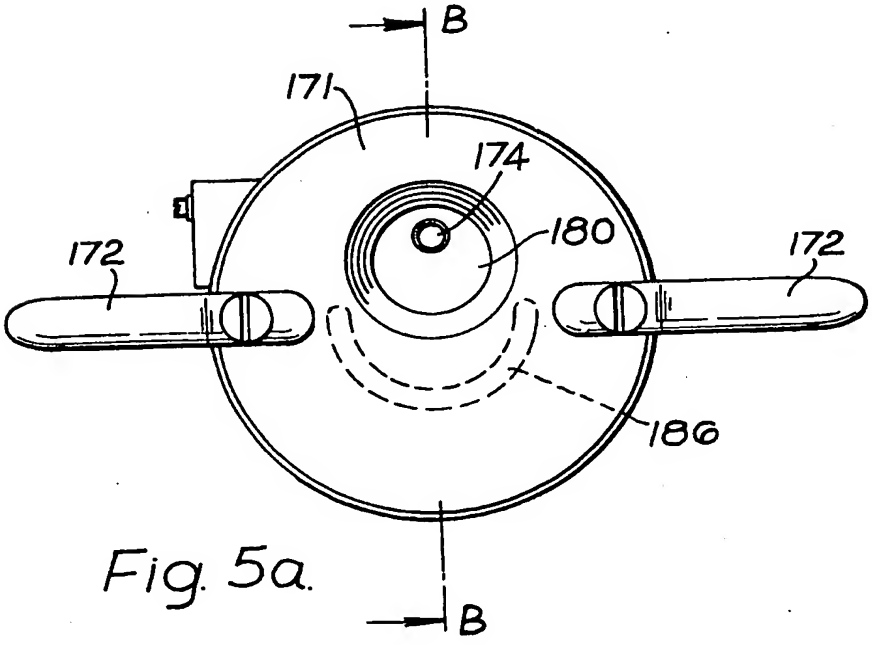

Fig. 5a.

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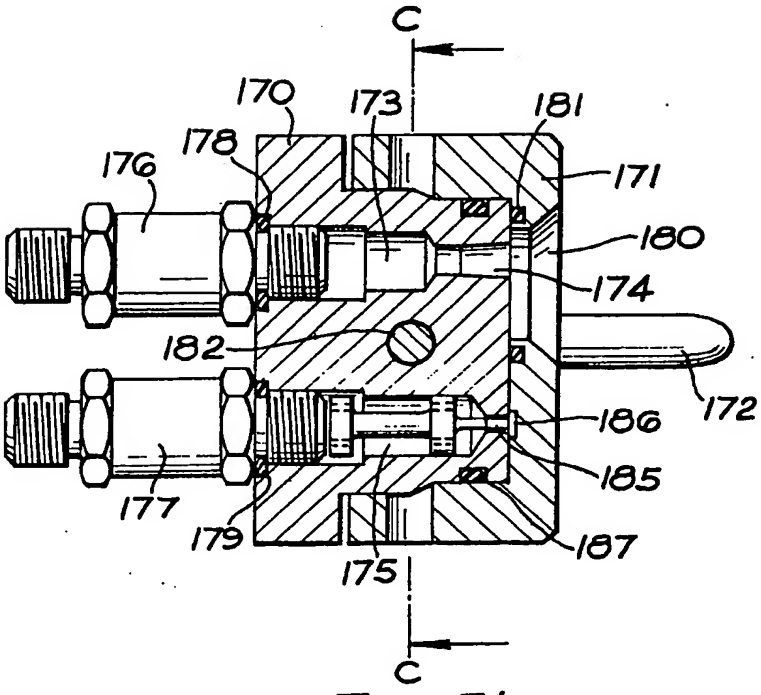

Fig. 5b

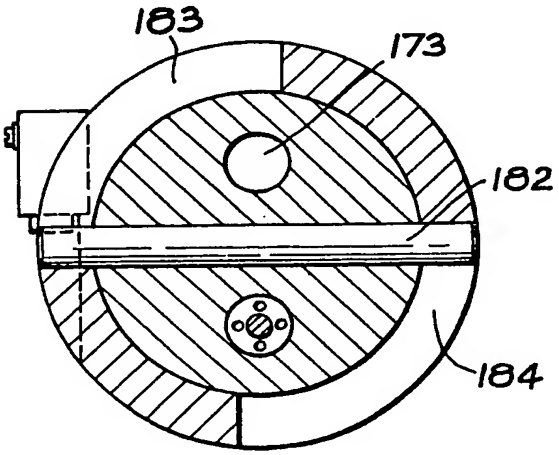

Fig. 5c.

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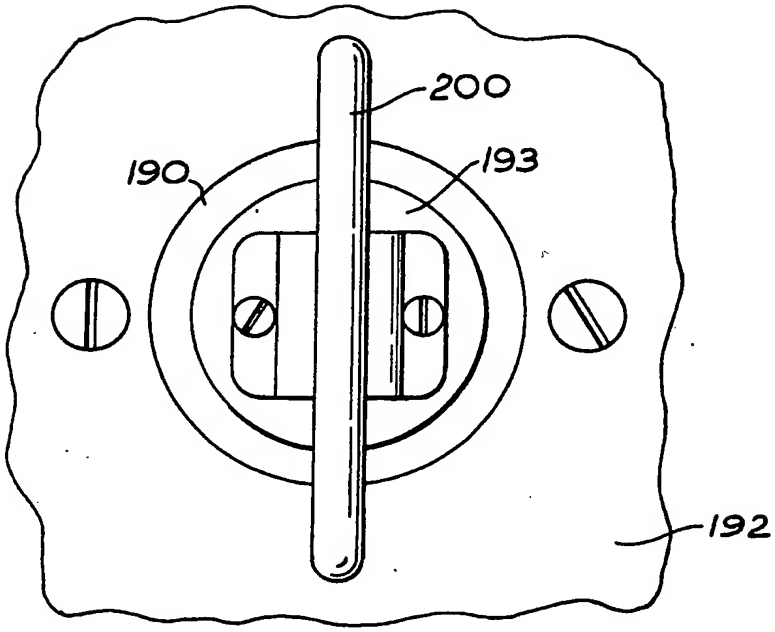

Fig. 6a.

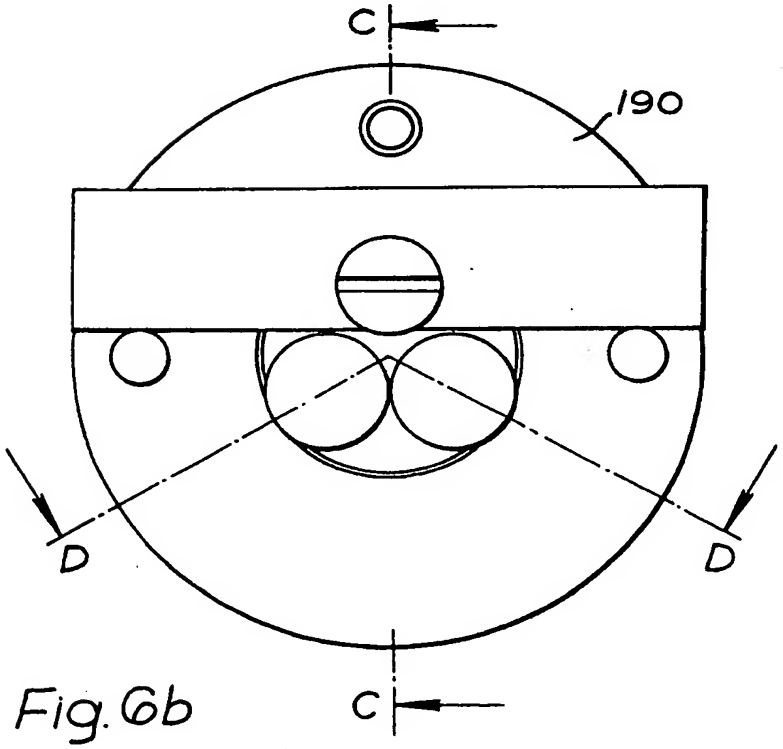

Fig. 6b

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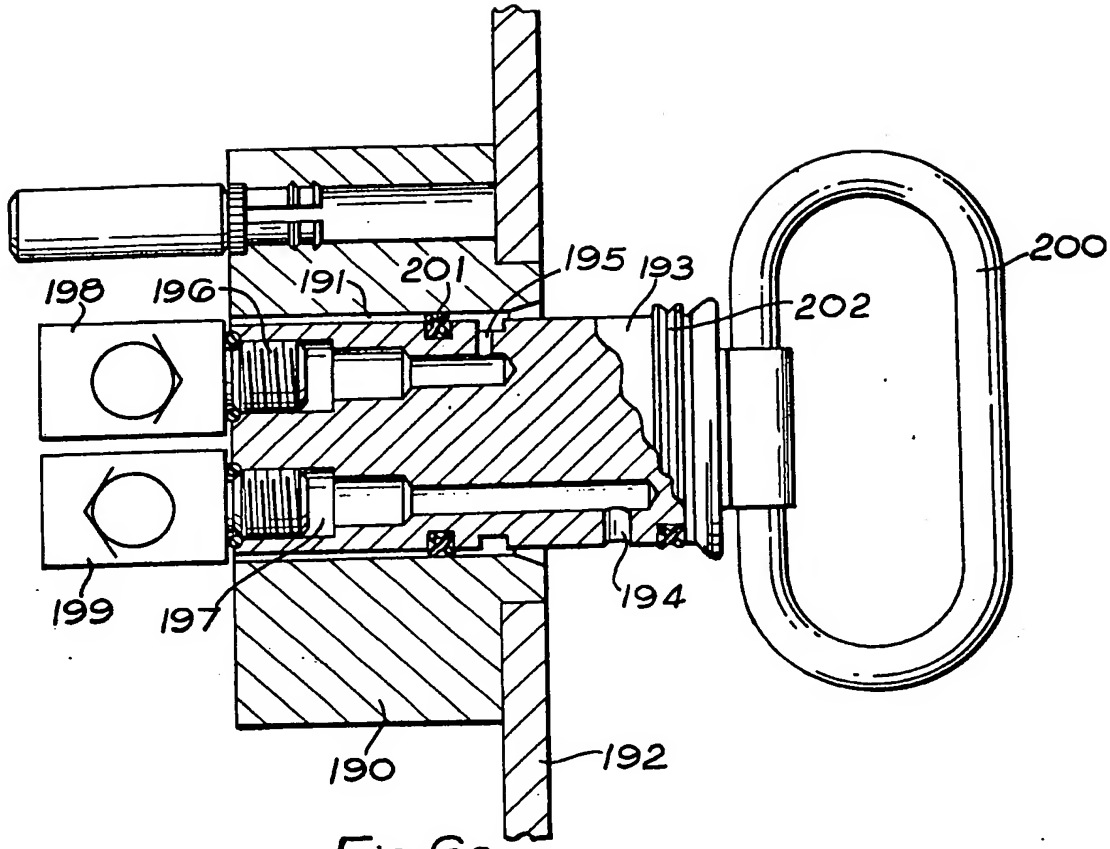

Fig. 6c.

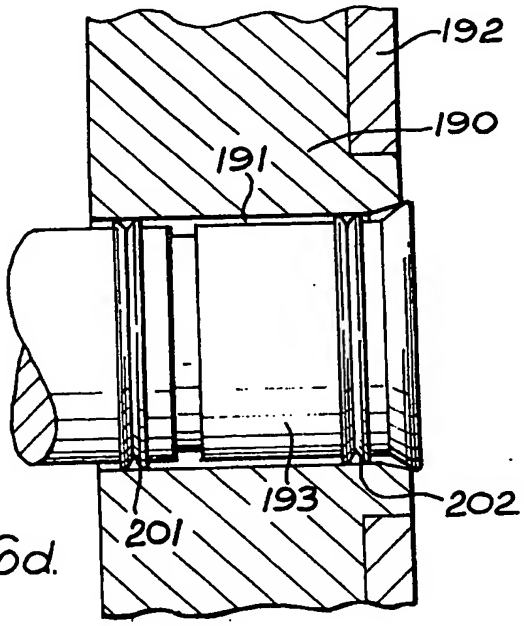

Fig. 6d.

SPECIFICATION

Production of solutions

The invention relates to a method and apparatus for producing sterile pyrogen free fluid for medical use.

Sterile pyrogen free fluid is often required in the medical field particularly for surgery. For example, transurethral resection (TUR) s relatively common operation for men involves passing a resectoscope through the penis along the urethra into the bladder and cutting away at the prostate gland by diathermy. For this purpose copious amounts of sterile pyrogen free fluid is required which must be electrically non-conductive (since diathermy is used) and which should also be isotonic or near isotonic to minimise fluid transfer with the patient. A commonly used fluid which meets the necessary requirements is a 1.5% solution of glycine in water and this is commonly supplied in sterile, sealed bags. The supply of glycine solution in this manner is not entirely satisfactory since the glycine solution is costly and the supply is possibly unreliable. Furthermore, such bagged (or bottled) fluid for this purpose has to be autoclaved after production, subjected to quality control procedures and finally warmed to body temperature before use. In use, bags are usually hung on a "drip-stand" and need to be connected aseptically to the resectoscope by means of a sterile giving set. The largest bag in use contains three litres and this means that several aseptic connections have to be made during one operation, each requiring the participation of hard pressed theatre staff and involving additional risk of infection.

To overcome the disadvantages of bagged or bottled sterile pyrogen free fluid it has already been proposed to prepare such fluid in situ by subjecting water to reverse osmasis to remove pyrogens and combining the pyrogen free water with a concentrated solution of glycine, the resulting mixture being sterilised before delivery to a collecting bag or bottling plant. Such a method and apparatus for performing the method are described in U.K. Patent Specification Nos. 1450030 and 1504334.

One disadvantage of the known method and apparatus lies in the fact that air remains in the water and concentrate mixture during the sterilisation phase. Such air, which may initially be in solution, is likely to form as air bubbles during the sterilisation process in which the moving fluid mixture is raised to a predetermined minimum temperature and maintained at that temperature for a predetermined minimum period of time. The presence of air bubbles may make the control of sterilisation difficult or impossible since the rate of fluid flow through a heating unit of the steriliser cannot be accurately monitored when air is present. The known method and apparatus do not provide for the removal of air from the mixture of water and concentrate so that adequate sterilisation cannot be guaranteed and, what is also undesireable a fluid mixture containing air bubbles may be delivered to the patent during an operation.

It is an aim of the present invention to overcome the above described disadvantages of known methods and apparatus for producing aqueous solutions for medical purposes.

According to a first aspect of the present invention, there is provided a method of producing sterile, pyrogen free aqueous solutions for medical use in which water is subject to reverse osmosis to remove pyrogens, the pyrogen free water is mixed with a fluid concentrate, such as glycine, and the mixture is sterilised, characterised in that air is removed from the mixture prior to sterilisation.

According to a second aspect of the present invention there is provided apparatus for producing sterile pyrogen free aqueous solutions for medical use comprising a reverse osmosis unit for producing pyrogen free water from water supplied, means for mixing said pyrogen free water with a fluid concentrate, de-aeration means for removing air from said mixture, and sterilisation means for sterilising said water and concentrate mixture.

Sterilisation may be performed in a sterilisation circuit into which the mixture of concentrate and pyrogen-free water is introduced prior to sterilisation. In this case it is advantageous to provide a pump in the sterilisation circuit in addition to a main pump elsewhere in the apparatus for pumping fluid through the apparatus. Such an additional pump would provide the advantages of allowing an increased flux of water through the reverse-osmosis unit (by making use of the full main pump pressure) whilst also allowing a desirable low pressure to be used for the de-aeration unit.

Advantageously sterilisation is achieved by raising the mixture to a sterilisation temperature and maintaining said temperature substantially constant for a predetermined time by allowing the fluid mixture to pass through a heat insulated chamber. The use of heat insulation instead of the thermostatically controlled supply of heat as in the known apparatus simplifies the apparatus and acts to conserve energy.

A spill valve, operative to open when fluid pressure exceeds a set value, may be situated prior to the means for mixing water and concentrate and connected to a return line such that water is delivered to the return line when the mixing means is unable to accept water supply (e.g. which is when the apparatus is in operative condition but not delivering sterilised fluid mixture). In this case, a heat exchanger may, advantageously as compared with the known apparatus, be provided for the exchange of heat between the sterilisation circuit and the return line. The heat exchanger serves to pass excess heat from the sterilising circuit to the water flowing in the return line when fluid in the sterilising circuit is being recirculated during periods when sterilised mixture is not being delivered by the apparatus. The heat exchanger also serves the function of extracting heat from the return line when pasteurisation of the apparatus is taking place prior to placing the machine in operative condition. During pasturisation, water at pasteurisation temperature is passed through the output line and bathes the output port of the apparatus before eventually flowing along

the return line. The heat exchanger extracts heat from this water in the return line, which heat would otherwise be largely wasted, and uses it to heat water in the sterilisation circuit where the water is raised to pasteurisation temperature for the pasteurisation phase.

In the known apparatus for producing sterile fluid mixture water is simply supplied to the reverse osmosis unit by a pump or simply at tap pressure, and water not passing through the membrane(s) is passed to drain. This gives a large consumption and wastage of water and it is therefore an advantage if, in the present invention, flow control means is provided in the drain line to limit the flow of waste water. Water having passed through the reverse osmosis unit but not passing to drain is recirculated so that a good flow of water over the membranes is always maintained. Because the flow control is effected at the drain, there is no input restriction to supply when the apparatus is being filled from the empty state.

Points at which bacteria or pyrogens may be introduced are the input connection for concentrate and the output for sterilised mixture. An advantage over the known apparatus may be obtained if the present invention is provided with input and output connectors which in their closed state provide a flow path for fluid to bathe the connection point when closed. Thus the input or output connector may comprise a tapered receptacle, or female connections, for a male counter part, the receptacle being disposed in a body enclosed in a relatively movable housing having two positions, one position giving easy external access to the receptacle, the other totally enclosing the receptacle and connecting it to an internal line in the apparatus. In the latter enclosed position, fluid, which would normally discharge from the receptacle, bathes the sides of the receptacle and the adjacent surfaces and returns to the apparatus via the internal line. During preparation sequences either for use or storage the normal production fluid may be replaced with a sterilant or disinfectant fluid (chemical or thermal) thus treating all surfaces which may come into contact with the external sterile connector attached to the giving line or concentrate input line.

Advantageously apparatus in accordance with the present invention is provided with means for monitoring the relative electrical conductivity of water on the two sides of the reverse osmosis membrane thereby maintaining a check on the efficiency of the membrane in reducing the ion concentration of water passing therethrough. The ability of such a membrane to remove ions, it should be noted, is impaired when the membrane becomes hydrolysed and it is important, as mentioned hereinbefore, to produce a final fluid mixture having a very low electrical conductivity.

Another advantage of the prior art may be obtained with the present invention by inclusion of means for flushing the system with formalin solution at shut down, said means comprising a dosing system for introducing a predetermined quantity of formalin concentrate and mixing it with retained fluid in the apparatus, said mixture being distributed throughout the apparatus for example at 1½% formalin solution. Preferably the formalin is taken from a reservoir by means of a venturi whose suction action is sufficiently great when flow of water through the venturi is encreased as a consequence of a drain valve being closed to terminate the flow of water to drain.

Instead, of known methods of monitoring fluid levels, (e.g. float switches, photo-electric cells, capacitance measurement etc.), use is advantageously made in the present invention of a method which is per se believed to be novel for an essentially non-conductive fluid. This method uses the infinitesimal conductivity of a liquid such as formalin to trigger logic devices of the field effect transistor (FET) type which have very high input impedances and effectively are purely voltage controlled devices. By the use of very high value resistors (of the order 1MΩ) disposed between supply and input very small currents (of the order of 1 μA) are sufficient to change the logic state of the inputs to such devices. These devices are supplied with low voltage DC so that the possibility of electroysis of the liquid is proscribed. Detection of liquid level may be achieved by the use of a probe comprising a plastics-coated wire with an end tip portion bored and located at the fluid level to be detected. of course, such FET logic devices may be used for detecting the levels of fluids which are conductive and comprise a relatively high ion concentration.

Means for mixing the pyrogen-free water with concentrate may be a proportioning pump which advantageously comprises four pistons, two large and two small, each with a respective chamber and arranged to reciprocate so that one large and one small piston take in fluid, this action being reversed at the end of each stroke. Each of the small pistons is connected with concentrate supply whilst the larger pistons are connected alternately and in antiphase with water supply and mixture output lines by means of a synchronously operated valve or valves.

The present invention will hereinafter be further described by way of example with reference to and as illustrated in the accompanying drawings in which:-

Figure 1 is a schematic circuit diagram of a urological fluid producing machine constructed in accordance with the present invention;

Figure 2 is a schematic diagram of a proportioning pump for use in the machine of Figure 1;

Figure 3a is a circuit diagram showing level detection circuitry for detecting normal maximum and minimum water levels in a break tank in the machine;

Figure 3b is a circuit for detecting abnormally low levels in the break tank;

Figure 4a is a circuit diagram of a device for detecting a minimum formalin supply for the machine;

Figure 4b is a circuit diagram of a device for detecting when a does of formalin has been taken into the machine;

Figure 5a is an end view of an input or output fluid terminal for the machine;

Figure 5b is a partial axial cross-section through the terminal of Figure 5*a* along line B-B of Figure 5*a*;

Figure 5c is a cross-section along line C-C of Figure 5*b*;
Figure 6a is a front elevation of an alternative embodiment of fluid terminal for the machine;
Figure 6b is a rear elevation of the terminal assembly of Figure 6*a*;
Figure 6c is part cross-sectional view of the terminal assembly of Figures 6*a* and 6*b*; and
Figure 6d is a partial cross-sectional view showing the assembly of Figures 6*a*, 6*b*, 6*c*, in a closed position.

Referring first to Figures 1, apparatus for producing a sterile pyrogen-free aqueous solution of glycine comprises a reverse-osmosis (R.O.) unit 10, concentrate supply means 11, a proportioning pump for mixing concentrate and post-R.O. water, and a sterilising circuit designated as a whole by numeral 12. Mains water is introduced into the system at an input 13 and passes through a filter 14 (to remove suspended matter) to a solenoid valve 15 which, according to whether it is open or closed, determines whether or not water is admitted to a break tank 16. A pump 17 pumps water to R.O. unit 10 by way of a filter 18, and water not passing through the membrane is either returned to the break tank 16 by way of a line 19 or passes to drain along a line 20 through a flow monitoring device 21 solenoid valve 22, non-return valve 23 and flow control device 24. Water having passed through the R.O. unit 10 flows along a line 25, through a filter 9 to a first input 26 of a proportioning pump 27. Concentrate from supply means 11 is able to flow by way of a connector assembly 28 and a non-return valve 29 along a line 30 to a second input 31 of proportioning pump 27 where pyrogen-free water and concentrate are mixed to provide a pyrogen-free aqueous solution which issues from an output point 32 along a line 33 and into the sterilisation circuit 12 by way of a non-return valve 34. Mixture passing into the sterilisation circuit 12 has air removed in a de-aeration unit comprising a heat exchanger 5, heater 6 and separation unit 7 before passing to a flow monitoring switch 35 and on to a pump 36 which serves to move mixture round the circuit 12. A heater 37 raises the temperature of the mixture to approximately 35°C, the mixture then passing through a heat exchanger 38 to a heater 39 and into a sterilisation unit 40. Mixture from the unit 40 again passes through heat-exchanger 38 and is able to pass out of the sterilisation circuit 12 along a line 41 through a filter 42 and solenoid valve 43 to an output connector assembly 44. When the connector assemby 44 is in the position shown in Figure 1, sterilised mixture is able to flow from an outlet port 45 through a tube 46 connected thereto and into a storage bag 47 for use, for example, in a surgical operation. When the connector assembly 44 is in a second position, the line from valve 43 is connected through the assembly 44 to a line 8 which returns to the drain line 20 so that formalin contaminated fluid is not recirculated but discharged from the machine. It will also be apparent that when concentrate input connector assembly 28 is in a second position, indicated schematically in Figure 1, line 30 communicates with a line 48 and thus, in accordance with the position of a solenoid valve 49, with output 32 to the proportioning pump 27. Alternatively valve 49 could be disposed so as to connect input 26 with line 30 with valve 28 in the second position.

A formalin dose mechanism 50, used in making up a formalin solution distributed throughout the apparatus at the termination of machine operation, comprises a formalin reservoir 51, a supply line 52 and a control valve 53, the line 52 being connected by way of valve 53 to the throat of a venturi 54 in line 19. The reservoir 50 has a dose chamber 55 formed by a disc partition 56 and this chamber 55 is vented to air by means of a tube 57. Line 52 extends down tube 57 and into dose chamber 55. A probe 58 senses whether there is sufficient formalin in the dose chamber to achieve formalisation of the apparatus whilst a further probe 59 senses when the formalin dose has been taken.

Operation of the apparatus will now be described. Assuming a formalin solution is distributed throughout the apparatus following previous use of the apparatus, this must first be thoroughly flushed from the machine. During the flushing operation only water is introduced (at inlet 13) into the machine which is operated with connector assemblies 28 and 44 in their respective alternative positions as seen in Figure 1. Water not passing through the R.O. membrane flushes the input line, break tank 16, half the R.O. unit 10 and the drain line 20 and elements therein. Water passing through the R.O. unit membrane is delivered to input 26 of proportioning pump 27 and also, by way of line 48 (valve 49 being in the open position), to input 31 so that the pump 27 mixes water from the two inputs and supplies this to sterilisation circuit 12. Water passes round the sterilisation unit and issues along line 41 to connector assembly 44 from where it passes to line 8 and then returns to drain. If initially valve 43 is closed the proportioning pump 27 does not accept fluid intake so that water passing from the R.O. unit 10 to filter 9 passes from that filter along a spill line 61 through a pressure operated spill valve 62 and along line 8 to drain. Provided a valve 63 is open for a portion of the flushing time to allow water circulation in the sterilisation circuit 12 to remove any formalin solution in that part of the circuit between the input and exit lines it will be clear that operation of the apparatus in this way with only water input leads to a complete flushing out of formalin. After flushing out the formalin the next phase of a preparation sequence is pasteurisation in which water in the apparatus is raised to 90°C or above in the sterilisation circuit and passed through the outlet connector assembly 44 to line 8. The connector assembly 44 is constructed such that when in its closed position (alternative position indicated in Figure 1), fluid flowing therethrough bathes the output connection point 45 and adjacent surfaces, so that pasteurisation of the output results from the pasteurisation phase. After pasteurisation glycine is introduced and the machine is run to distribute glycine solution throughout the machine. At this time the connector assembly 28 is open for the introduction of glycone concentrate whilst connector assembly 44 remains closed and glycine solution having been prepared by the proportioning pump 27, circulated round the sterilisation circuit 12, and delivered to connector assembly 44 passes along line 8 to drain line. Simultaneously with distribution of glycine through the apparatus in this way, the temperature in the

sterilisation unit 40 is raised above 135°C and the delivery temperature is brought to 37°C to 40°C. The outlet connector assembly may be connected to line 46 after a minimum sterilisation period has been completed and storage bag 47 (sterile) is filled until a "bag full" signal closes solenoid valve 43, while opening valve 63. The signal that bag 47 is full is provided in the present example, by a switch 64 actuated when the weight of the bag reaches a predetermined value.

Water introduced in input 13 passes through filter 14, which as mentioned hereinbefore, act to remove any suspended matter. To keep a check on the state of filter 14, i.e. to find whether or not it is becoming blocked, a switch 65 actuated in response to a predetermined pressure drop is connected across the filter. When the filter becomes blocked the switch 65 provides a signal to a monitoring display (not shown) of the apparatus. A variable orifice 66 is disposed in a line to the switch and may be closed to test that the switch 65 is functioning. To enable fluid pressure to fall in a section of the switch when orifice 66 is closed a further bleed orifice 67 is provided in a line 67 from the switch 65 to break tank 16. The level of water in the break tank 16 is controlled by means of two level detecting probes 69 and 70. Probe 69 is "water full" probe which detects when the water level is at a maximum desired value and acts by means of appropriate circuitry (described hereinafter) to close valve 15 when the water level reaches that maximum value. Probe 70 is a "water fill" probe which defines a level below which valve 15 is opened to allow the flow of water into the tank 16. There is thus a degree of hysteresis designed into the system in that fresh water is not introduced into tank 16 until a level determined by probe 70 is reached whilst when indicated this fresh supply of water is not terminated until a level determined by probe 69 is reached. This ensures that valve 15 is not constantly being opened and closed. A probe 71 at a lowermost level determines when the water level falls to a dangerous level and is operative to sound an alarm. We mention here the fact that water supply pressure is monitored by a pressure gauge 72.

Water from tank 16 is pumped by pump 17 through filter 18 and here again the pressure difference across the filter is monitored by a switch 73 actuated when a predetermined pressure difference is attained. In this case too a variable orifice 303 is placed in a line on one side of the filter 18 to allow testing, a further small bleed orifice 304 being disposed in a line from one side of switch 73 to the break tank 16. One important difference however is the provision of a line 305 from the other side of switch 73 to the break tank return line. A restricting or bleed orifice 306 is placed in line 305 to allow a small but steady flow through line 305. This arrangement ensures that when formalin is being flushed from the system it is also flushed from the valve 73 and connecting lines thereto. It is one of the novel and inventive features of the apparatus described that there are no "dead ends" to interfere with and/or prevent full formalisation or flushing of formalin from the system. Further, complete pasteurisation of all relevant portions of the apparatus is allowed. Water passing through the R.O. unit 10 without passing through the membrane is split into two portions, one of which (the greater) returns to the break tank 16 while the other flows along line 20, out of the machine to drain. The flow of water to drain is set and maintained constant irrespective of fluid pressure by means of the flow control device 24.

In this way no undesirable restriction is placed on the input flow whilst a good compromise can be obtained between efficient operations of the R.O. unit 10 and minimum wastage of potable water. A relative conductivity monitoring device 74 compares the electrical conductivites of water on each side of the membrane of the R.O. unit 10. A decrease in the relative conductivites indicates a fall-off in the efficiency of the membrane (probably through membrane hydrolysis) in reducing ion concentration. Normally only about 5% of ions in the water are transmitted through the membrane.

Water passing out of the R.O. unit 10 is pyrogen-free and has a greatly reduced ion concentration. This water passes through filter 9 (pressure again being monitored across the filter, here by a switch 76) and to the proportioning pump 27 which mixes water and concentrate in predetermined proportions. It will be noted that switch 76 is connected so that the main flow of fluid passes through both sides of the switch so there is no problem here posed by dead spaces requiring special arrangements for flushing. Switch 73 is connected as previously described since the fluid flow (main flow) is too high at that point to pass through both sides of the switch. Mixture delivered by pump 27 to sterilising circuit 12 is de-aerated in de-aerator 5, 6, 7 and passes to low pressure pump and on to a heat exchanger 77. The de-aerator operates by heating the fluid to below boiling point and allowing air to bleed out of unit 7 (preferably by way of a float valve to prevent fluid loss) along a line 3 to a line 4 connected to formalin line 52 which is sterile and under low pressure by virtue of venturi 54. A variable aperture 78 connected across pump 36 enables the output pressure and flow of the pump to be matched to the requirements of circuit 12. Fluid heated to 36°C by heater 37 enters heat exchanger 38, where it picks up heat from fluid leaving steriliser unit 40, and reaches a temperature of approximately 130°C before entering heater 39 which again raises its temperature this time to a sterilisation temperature of approximately 138°C after which the fluid enters the heat insulated steriliser unit 40 where it remains, in its slow passage around the circuit 12, for a period of about 4.5 minutes. Sterile fluid leaves the steriliser at about 136°C and enters heat exchanger 38, giving up heat to incoming fluid, and leaves heat exchanger 38 at a temperature of approximately 39°C. If valve 43 is open, fluid is delivered to bag 47 provided the pressure is sufficient to open a pressure operated valve 81. Fluid taken from the sterilisation circuit 12 is made up by fresh mixture supplied by the proportioning pump 27. When valve 43 is closed (bag 47 full) valve 63 is open and fluid in the sterilisation circuit 12 continues to circulate in a re-circulate mode. Alternatively valve 43 and 63 may be replaced by a single 3-way valve positioned at the circuit junction between 81 and 63. Since the proportioning pump 27 is unable then to deliver fluid to the sterilisation circuit

it is unable to accept either water or concentrate and in particular water supplied through line 25 is spilled from filter 9 to line 8 which returns to it to drain. The water thus passing along line 8, passes through heat exchanger 77 and absorbs heat from the recirculating fluid in sterilisation circuit 12. Since it is necessary to control the temperature at the input to heat exchanger 38 somewhat lower than the desired delivery temperature an unstable situation would arise with a progessive increase in delivery temperature unless the recirculated fluid were cooled in this way by heat exchanger 77. This heat exchanger 77 serves a dual purpose since in the pasteurise phase the temperature of fluid delivered to the outlet of circuit 12 is temporarily raised to above 90°C and this fluid is taken by way of exchanger 77 to drain. During the passage of the pasteurising fluid through exchanger 77, heat is extracted by fluid in circuit 12. Thus, much of this otherwise wasted heat is returned to the fresh fluid passing to heater 37. There is very little spill from valve 62 during this operation condition so that the efficiency of the thermal recovery is very little impaired.

At the end of the operation of the apparatus formalin solution is distributed throughout. In contrast with, the prior art, and advantageously with respect thereto, formalin solution as such is not introduced into the machine. Instead a dose of formalin is introduced and this is mixed with fluid in the machine and pumped through the whole apparatus. To introduce a dose of formalin the drain valve 22 must be closed so that the flow of water through conduit 19 increases to such a level that the suction at the throat of the venturi 54 is sufficient, when valve 53 is open, to take formalin from dose chamber 55 of the formalin reservoir 51. This formalin flows through conduit 19 and into break tank 16 where it mixes with water therein. From the break tank the formalin solution is pumped throughout the machine and during this period connector assemblies 28 and 45 are in their closed (return loop) positions and valves 43 and 49 are open. Thus formalin solution is fed to both inputs of the proportioning pump 27 which pumps the solution to circuit 12 from where it is fed to connector assembly 45 and returns along line 8 to drain.

The formalin reservoir 51, as previously described, has a probe 58 which detects a minimum fluid level in dose chamber 55 and provides an enable signal for the starting of the machine. The probe 59 detects the level in chamber 55 when a dose has been taken and is operative to terminate formalin flow. The partition 56 which separates the dose chamber 55 from the rest of the reservoir 51 has a small orifice 82 through which formalin drips to fill the dose chamber. The make-up flow through orifice 82 is slow compared with the rate of removal by venturi 54 during dosing so that it does not significantly affect the dose taken, but ensures that the dose chamber refills in good time for the next formalisation. Alternatively orifice 82 may be omitted and two-way valve 53 replaced by a three-way valve which in the normal resting condition connects the dose chamber 55 with the reservoir 51 and when actuated connects the dose chamber to the venturi 54. It should be noted that though formalin is injected on only one side of the membrane of the R.O. unit, formalisation occurs throughout the machine since formalin passes freely through membranes used in reverse osmosis. This arrangement is advantageous over the prior art in which formalin is injected both sides of the R.O. membrane.

The proportioning pump 27 will now be described in more detail with reference to Figure 2 of the drawings. The pump comprises four pistons 90, 91, 92 and 93 mechanically coupled in a housing 94 such that two similar large pumping chambers 95, 96 and two smaller pumping chambers 97, 98 are pumped with one of each in phase and the other pair in anti-phase. Movement of the multiple piston assembly in one direction will cause simultaneous displacement of fluid from one of each large and small pumping chambers (say 96, 97) and induction of fluid into the other pair. Reversed movement results in the displacement and induction processes being interchanged. Water is supplied to the input point 26 which branches to two solenoid valves 99 and 100 actuable in antiphase in accordance with the position of the multiple piston assembly. Proximity sensors 101 and 102 actuate a switch 103 when pistons 90 and 93 reach the end of their respective strokes and switch 103 is operative to reverse the positions of the valves 99 and 100. With valves 99 and 100 in their illustrated positions pyrogen-free water (i.e. permeate, or post-R.O. unit water) is introduced into cylinder 95 through valve 100 as the multiple piston assembly moves to the left as seen in Figure 2. Glycine concentrate is introduced to input 31 which branches to two lines leading by way of respective non-return valve 104 and 105, to the small pumping chambers 97 and 98. As the piston assembly moves to the left glycine concentrate passes through valve 105 into chamber 98 and at the same time glycine concentrate is pumped out of chamber 97 through a non-return valve 106 and is mixed with water pumped from large chamber 96, the mixture passing out along outlet line 33. When the piston assembly reaches the extreme left, the positions of the solenoid valve 99 and 100 are reversed and water is introduced into chamber 96 through valve 99 whilst glycine and water mixture is pumped through valve 100 to line 33, the glycine being pumped out of chamber 98 through a non-return valve 107 to mix with the water being pumped from chamber 95. It will be appreciated that since water supplied at input 26 is under relatively high pressure, the piston assembly is in fact, driven in its reciprocating movement by this pressure. The proportioning pump is thus a passive element in the apparatus and since there is in effect no interruption, in the supply of water (and concentrate) and no interruption in the output of mixture, the pump appears as a simple resistance connecting feed and exhaust. The mix ratio (of concentrate to permeate) is, of course, governed solely by the relative cross-sectional areas of the large and small pistons. Solenoid valve 49 (see also Figure 1) is connected to line 48 between concentrate input line and mixture exhaust line 33. When this valve is closed there is no effect on the proportioning system, but when opened it allows exhaust mixture to be fed back to the concentrate feed line provided that the exhaust pressure is the higher. The non-return valve 29 prevents exhaust mixture entering the concentrate reservoir. By selectively opening valve 48 for

some or all of the states of the proportioning pump the mixing strength may be reduced progessively towards zero. The opening and closing of valve 48 may be achieved from signals derived from proximity sensors 101 and 102 through preferably a signal derived from an independent device such as an integrated circuit timer delivering a square wave with selectively variable period ratio of "on" to "off" ("high" to "low") states may be used. A further non-return valve 29 connected between valve 49 and input line 30 allows variable proportioning to take place whilst remaining closed in preference to valve 29 (which has a lower opening pressure) during flushing of assembly 28. The use of valve 48 will, of course, result in imperfect mixing and may require the addition of a mix chamber 109 in the exhaust line. As an alternative arrangement the permeate input line (leading to input 26) could be connected to the concentrate input line by way of a solenoid valve similar to valve 48. In a further variation, the ability to adjust the concentration of solution leaving the pump, may be achieved mechanically. Thus the two lines branching from input 31 after non-return valves 104, 105 and leading to chambers 97 and 98 may be bridged by a control cylinder containing a freely movable control piston, the extent of the movement of the freely movable piston being variable mechanically, for example by a movable stop. In this latter case the freely movable piston is reciprocated and is displaced by concentrate pumped by piston 90 or 93 into the control cylinder preferentially to pumping to exhaust until the piston movement is halted by a stop or an end of the control cylinder whereupon the remaining concentrate in the cylinder 97 or 98 is pumped to exhaust. By varying the travel of the control piston between zero and a maximum value the fluid concentration at exhaust may be varied between a maximum value and a minimum (which may correspond to pure permeate if the travel of the control pin is not halted during the movement of the multiple piston assembly.

Referring now to Figures 3*a* and 3*b* the means for detecting fluid levels in the break tank 16 will be described in detail Figure 3*a* shows the circuit for detecting the normal maximum and minimum fluid levels. Probe 69 for detecting the maximum fluid level is electrically connected to an input 110 of a NAND gate. A second NAND gate 112 is connected to gate 111 to form a cross-over latch with an output 113 connected to a second input 114 of gate 111. An output 115 (forming the output of the latch) is connected to a first input 116 of gate 112. Probe 70 for detecting minimum fluid level in the break tank 16 is connected to an input 117 of a NAND gate 118 a second input 119 of which is connected to the input 117. The output 120 of gate 118 is connected to a second input 120 of logic gate 112. Input 110 of gate 111 is connected through a high value (e.g. 1.2 MΩ) resistor 121 to a supply voltage rail 122 maintained at a fixed low voltage (say 5V) representing a logic "high". Input 117 of NAND gate 118 is also connected to the supply voltage through a similar high value resistor 123. The output 115 of the cross-over latch is connected through a protection resistance 124 to the base of an NN transistor 125, the collector-emitter line of which is connected between the rail 122 and a digital ground line 126. A relatively low value resistor 127 is disposed in the collector line of transistor 125 whilst a relatively high value resistor 128 is connected between collector and emitter. The transistor 125 is able to control power transistor 129 by virtue of an electrical connection between the collector of transistor 125 and the base of transistor 129. Transistor 125, it will be appreciated, provides a buffer which electrically separates the low current digital logic circuitry from the power circuit operating the break tank valve.

Each of the NAND gates 111, 112, and 118 forms part of an integrated circuit in which the transistors are of the field effect type e.g. MOSFET. Field effect transistors have very high input impedances so that the logic gates may be considered as purely voltage operated. The operation of the circuit of Figure 3*a* will now be described.

The truth table for the cross-over latch formed by the logic gates 111 and 112 is as follows:

INPUT 110	INPUT 120	OUTPUT 115
HIGH	HIGH	HIGH OR LOW
HIGH	LOW	LOW
LOW	HIGH	HIGH
LOW	LOW	HIGH

If initially the fluid level in break tank 16 lies above the position of probe 69 current flows through the fluid between probe 69 and earth and between probe 70 and earth. The earth may be provided by a common ground probe disposed towards the bottom of the tank. Since the fluid resistance is small compared to the very high value resistors 121 and 123, current flow brings both input 110 and input 117 to "low" levels. Since input 117 (to NAND gate 118) is low, input 120 to the cross-over latch is high. Thus output 115 is high, transistor 125 conducts and transistor 129 is maintained in a non-conducting state, valve 15 stays closed and no water is admitted to the break tank 16. When the fluid in tank 16 falls below probe 69 input 110 becomes a "high", input 120 remains "high" and output 115 remains in its previous state so that velve 15 is maintained closed. When the fluid level falls below probe 70 input 120 becomes "low" (NAND gate 118 acts as an inverter) so that output 115 becomes "low", transistor 125 is switched off, transistor 129 conducts and valve 15 is opened to admit water to tank 16 whereupon the fluid level rises above the level of probe 70 and

continues rising (output 115 remaining in the low state) until the fluid level reaches probe 69. The system thus has a degree of hysteresis in that water inflow, once initiated, is not terminated until the fluid level has risen a substantial amount. Similarly fluid level may fall from the level at which inflow was terminated, by the same substantial amount before water is again introduced. This saves the water supply arrangement from constantly switching on and off in response to minor fluctuations in fluid level.

Probe 71 is located below probes 69 and 70 and is connected to an input 132 of a NAND gate 133, as may be seen from Figure 3*b*. Input 132 is connected to the digital voltage supply line through a high value resistor 134 and a second input 135 is connected directly to the supply voltage. An output 136 is connected through a current limiting resistor 137 to the base of a transistor 138 whose collector voltage is used to actuate an alarm. When the water level in tank 16 falls below probe 71 input 132 to gate 133 becomes "high" to produce a "low" at output 136 which switches transistor 138 off so that the collector voltage becomes "high" to trigger an alarm.

The formalin dose chamber 55 is provided with the fluid level probes 58 and 59. Referring to Figure 4*a* it will be seen that probe 58 is connected to an input 140 of a NAND gate 141 whose other input 142 is connected to the digital supply line 122. Input 140 is also connected to line 122 through a high valve resistor 143. An output 144 is connected through resistor 145 to the base of a transistor 146. Output 144 is also connected through a resistor 147, to the base of a transistor 148 controlling current through a relay 149. Provided the formalin level is above the probe 58, current flow through resistor 143 is sufficient to bring input 140 to a "low" level so that output 144 is "high" transistor 146 is conducting and this provides an enable signal to a logic circuit (not shown) which allows the apparatus as a whole to be started. Similarly transistor 148 is conducting, relay 149 is actuated and a switch 150, "normally closed", is maintained open so that a "formalin empty" lamp is not lit. Should the formalin level be below the level of probe 58 prior to an instruction to open valve 53 to introduce formalin into tank 16 then output 144 is high, transistor 146 ceases to conduct and an enable signal is not produced. Thus if there would be insufficient formalin to close down the apparatus at the end of operation, the apparatus may not be started at all. Further, transistor 148 is switched off and switch 150 is allowed to close thereby lighting a warning lamp indicating insufficient formalin for formalisation. Referring to Figure 4*b*, probe 59 is connected to the joined inputs 152 and 153 of a NAND gate 154 (which like all other gates described, comprises field effect transistors). An output 156 is connected to an input 157 of a cross-over latch formed from two NAND gates 158 and 159. Another input 160 of the latch is connected through a high valve resistor 161 to the logic supply voltage line. Output 162 of the latch is connected to the base 163 of a PNP transistor 164. Capacitors 300 and 301 connected respectively between an input of gate 154 and earth, and an input of gate 159 and earth ensure that the inputs 153 and 160 to these gates are low at the instant the apparatus is switched on. Thus inputs 157 and 160 to the cross-over latch are initially high and low respectively so that output 162 is low and transistor 164 is conducting. If the formalin level is above probe 59 the input 157 remains high, input 160 rises to high as capacitor 301 charges and output 162 remains low and transistor 164 remains conducting. If a dose is taken from the dose chamber of the formalin reservoir so that the formalin level falls below probe 59 latch input 157 becomes low and output 162 becomes high to switch off transistor 164 so that the collector voltage (taken to a logic circuit, not shown) falls from high to low and formalin supply to the break tank is discontinued. As the formalin level rises in the dose chamber input 157 becomes high but output 162 remains high (the truth table for the latch is identical to the truth table for the latch in Figure 4*a*) so that transistor 164 remains non-conducting and this state in only reversed when the machine is next switched on at the start of operation of the whole apparatus.

Referring now to Figures 5*a* and 5*b* and 5*c* a first embodiment of connector assembly is illustrated which comprises a stainless steel body portion 170, and an end cap 171 also of stainless steel fitted to the body portion 170, and handles 172 for turning the end cap relative to the body portion. The body portion has an axially parallel bore 173 with a tapered portion 174 at the cap end to form the female portion of a standard Luer connection, portion 174 providing an outlet (or inlet) of the connector assembly. A return bore 175 is also provided in the body portion, parallel with bore 173. Non-return valves 176 and 177 are fitted to bores 173 and 175 and seals are provided by O-rings 178 and 179 respectively. The cap 171 has a window 180 which aligns with port 174 giving access for external connection with a sterile male Luer. The window is sealed to the face of the body portion by means of an O-ring 181. The cap 171 is prevented from separating from the body by means of a pin 182 passing diametrically through the body and engaging at each end a respective one of circumferential slots 183 and 184 in the cap. The slots allow rotation of the cap 171, relative to the body portion 170, through 90° so that the window 180 is taken out of alignment with port 174 which is brought into sealed communication with a return port 185, this being the end of bore 175. A groove 186 on the reverse of the cap 171 gives a good flow passage between ports 174 and 185 and O-ring 181 together with a further O-ring 187 prevent external leakage. Window 180 is chamfered to improve access and is offset downwards relative to port 174 to avoid bridging of sterile to non-sterile surfaces by drops of fluid. Thus it will be understood that when window 180 is aligned with port 174 and when cap 171 is turned through 90°, port 174 is placed in communication with port 185 so that fluid (for example during pasteurisation or formalisation phases of the whole apparatus operation) may flow between the two ports in particular bathing port 174 as it does so. The illustrated connector assembly may thus be used at the apparatus outlet and/or at the input for glycine (or other) concentrate though when used at the glycine input valve 176 would be replaced by a valve acting in the opposite sense, whilst valve 177 would be omitted.

Referring finally to Figures 6*a*, 6*b*, 6*c* and 6*d*, an alternative output or input connector comprises a housing

190 with an accurately machined bore 191, the housing being mounted in a frame 192 of the machine. A central cylindrical plunger 193 has radial ports 194 and 195 communicating by means of axially parallel bores 196 and 197 with non-return valves 198 and 199. The plunger 193 has a handle 200 for moving the plunger between the open position shown in Figure 6*c* and the closed position of Figure 6*d*. In the open position radial port 194 is exposed. Port 194 is tapered to correspond to a standard male Lver connector. The other radial port 195 remains within the bore 191 of the housing 190. In the closed position both radial ports 194 and 195 lie within the bore 191 and are in fluid communication with each other by means of the contained volume represented by the diametral clearance between plunger and bore and two annular seals 201 and 202. In the closed position fluid issuing from port 194 passes around the outer surface of the plunger and re-enters the machine by way of port 195. The non-return valves 198 and 199 ensure that no reversal of flow direction can occur when the connector assembly is used, as in this case, as an output terminal from the machine. This assembly may of course, like that of Figures 5*a*, 5*b*, and 5*c* be used as an input connector assembly, though again modification or omission of the non-return valves would be required.

It is not considered that the present invention is limited in its aspects to a method or an apparatus for producing aquesous solutions. A further aspect of the invention is a proportioning pump comprising a multiple piston assembly adapted for reciprocating movement each in a respective cylinder such that at least a pair of said pistons move in phase with one another and in antiphase with a further pair of said pistons, the further pair moving in phase with one another, each pair of pistons being adapted to alternately induct two fluids, one into each corresponding cylinder of each piston of the pair and to pump said inducted fluids for producing a mixture of said fluids.

Still a further aspect of the present invention is a connector assembly adapted for actuation between two states, said assembly having a delivery or reception line with a connection region exposed for connection to an external fluid line when when the assembly is in a first of said states, and a further fluid line which is closed when the assembly is in said first state and which is connected to said delivery or reception line when the assembly is in a second state with the delivery or reception region not exposed for external fluid line connection, a fluid path being thereby defined between said delivery or reception line and said further line such that the connection region is bathed by the flow of fluid therebetween.

CLAIMS

1. A method of producing sterile, pyrogen-free aqueous solutions for medical use in which water is subjected to reverse osmosis to remove pyrogens, the pyrogen-free water is mixed with a fluid concentrate, such as glycine, and the mixture is sterilised, characterised in that air is removed from the mixture prior to sterilisation.

2. A method as claimed in claim 1 wherein sterilisation is performed in a sterilisation circuit through which the mixture of water and concentrate is pumped by a pump other than a main pump.

3. A method as claimed in claim 1 or 2 wherein sterilisation is achieved by raising the temperature of the mixture.

4. A method as claimed in claim 3 wherein the mixture is maintained at a raised temperature for a predetermined time by passing it through an insulated enclosure.

5. A method as claimed in any preceding claim, wherein water is fed to a semi-permeable membrane for said reverse osmosis and at least part of the water not passing through the membrane is recycled to join feed water to the membrane.

6. A method of producing sterile, pyrogen-free aqueous solutions for medical use substantially as hereinbefore described with reference to and as illustrated in the accompanying drawings.

7. Apparatus for producing sterile, pyrogen-free aqueous solutions for medical use, comprising a reverse osmosis unit for producing pyrogen-free water, means for mixing pyrogen-free water with a fluid concentrate, de-aeration means for removing air from said mixture, and sterilisation means for sterilising the water and concentrate mixture.

8. Apparatus as claimed in claim 7, and having a main pump for circulating liquid around a system of conduits, an additional pump being provided for pumping the mixture through a sterilisation circuit, part of the system, constituting the sterilising means.

9. Apparatus as claimed in claim 7 or 8, wherein the sterilisation circuit includes a heater capable of raising the temperature of the mixture to a sterilisation temperature.

10. Apparatus as claimed in claim 9, wherein the sterilisation circuit includes an insulated enclosure for maintaining the mixture at sterilisation temperature for a predetermined time.

11. Apparatus as claimed in claim 8, 9 or 10 wherein a pressure-sensitive spill valve is provided prior to the means for mixing the water and concentrate and is connected to a return line such that water is delivered to the return line when the mixing means cannot accept water supply.

12. Apparatus as claimed in claim 11, wherein a heat exchanger is provided for transferring heat between the sterilisation circuit and the return line.

13. Apparatus as claimed in any of claims 7 to 12, wherein overflow water leaving the reverse osmosis unit without passing through the membrane is conducted to a drain via a flow control unit which allows only a predetermined flow to the drain, returning any water above this quantity to a water inlet feed line.

14. Apparatus as claimed in any of claims 7 to 13 and having input and output connectors which, when

closed provide a fluid flow path which enables them to be bathed in a sterilant or disinfectant fluid when the apparatus is not in use.

15. Apparatus as claimed in Claim 14, wherein the input and output connection(s) each comprises a tapered receptacle or female connection, for a male counterpart, the receptacle being disposed in a body enclosing a relatively movable housing having two positions, one position giving easy access to the receptacle, the other totally enclosing the receptacle and connecting it to an internal line of the apparatus.

16. Apparatus as claimed in any of claims 7 to 15 and further including means for monitoring the relative electrical conductivity of the water on each side of the membrane in the reverse osmosis unit.

17. Apparatus as claimed in any of claims 7 to 16 further including means for flushing the system with sterilant or disinfectant solution upon shut-down.

18. Apparatus as claimed in claim 17, wherein said means comprises a closing system for introducing a predetermined quantity of formation concentrate and mixing it with fluid maintained in the system to fill the whole system.

19. Apparatus as claimed in claim 18, wherein the formation is taken from a reservoir by means of a venturi.

20. Apparatus as claimed in any of claims 7 to 19, wherein liquid level detection in the system is effected by conductive probes connected to logic devices of the field effect transistor type.

21. Apparatus as claimed in claim 1, wherein each probe is in the form of an insulated conductor having a bared end.

22. Apparatus as claimed in any of claims 7 to 21, wherein the means for mixing the pyrogen-free water with concentrate is a proportioning pump.

23. Apparatus as claimed in claim 22, wherein the proportioning pump comprises four pistons, two of which are larger than the other two, each having a respective chamber and arranged to reciprocate so that one large and one small piston take in fluid, this action being reversed at the end of each stroke, each of the small pistons being connected to a concentrate supply whilst the larger pistons are connected alternately and in antiphase with water and mixture output lines by means of one or more synchronously open valves.

24. Apparatus for producing sterile pyrogen-free fluid for medical use substantially as hereinbefore described with reference to and as illustrated in the accompanying drawings.

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